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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/685,061	ROBL ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed May 30, 2002, Paper No. 11, has been entered. Claims 1-50 have been cancelled; claims 51-132 have been added. Note that there is a duplicate claim 130, as such, the claims have been renumbered by Rule 1.126.

Any rejection made of record in the prior Office action, mailed 1/30/2002, Paper No. 9, and not made of record in the instant Office action, has been withdrawn in view of Applicants' amendments to the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-25 and 31-35 of copending Application No. 09/809,018. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant

application is directed to a method of cross-species nuclear transfer using differentiated human or mammalian cell or cell nucleus and an enucleated animal oocyte, culturing the nuclear transfer unit and isolating cells from the resulting blastocyst; and the '018 Application is directed to a method of producing embryonic or stem-like cells by a method of producing a nuclear transfer unit and obtaining embryonic or stem-like cells from the nuclear transfer unit. As such, the instant claims are made obvious by the '018 Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 51-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-14, 17-19, 21-23, 32-35, 51-57, 60 and 61 of copending Application No. 09/260,468. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is directed to a method of cross-species nuclear transfer using differentiated human or mammalian cell or cell nucleus and an enucleated animal oocyte, culturing the nuclear transfer unit and isolating cells from the resulting blastocyst; and the '468 Application is directed to methods of producing embryonic stem-like cells from a nuclear transfer unit using a differentiated human or mammalian cell and an enucleated animal oocyte. As such, the instant claims are made obvious by the '468 Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims from Application Serial No. 09/874,040 were not available for consideration of obviousness-type double patenting.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-78, 86-111 and 125-127 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for producing a nuclear transfer unit having genomic DNA of one mammalian species and mitochondria of a different mammalian species, comprising: (i) removing the genomic DNA from a mammalian oocyte; (ii) inserting a differentiated mammalian donor cell, or the nucleus of said cell, into the oocyte under conditions suitable for the formation of a nuclear transfer unit so that a nuclear transfer unit is formed, wherein said oocyte and said differentiated cell are from different mammalian species; (iii) activating the resultant nuclear transfer unit; and (iv) culturing the activated nuclear transfer unit to produce a multicellular structure.

The specification discloses the preparation of nuclear transfer units via a method of nuclear transfer of adult human epithelial cell nuclei into enucleated cattle oocytes to form a nuclear transfer (NT) unit (Figure 1) by electrofusion techniques. The methods disclosed in Example 1 of the specification result in the production of 1 NT unit (16-400 cell stage) according to Table 1, page 42. The specification further teaches that interspecies NT can be used to clone a gaur using cross-species nuclear transfer into an enucleated bovine oocyte, with normal karyo- and phenotypic development through attachment and later stages of fetal growth, with the differentiation of complex tissues and organs (see Example 2, p. 43). In particular, the specification teaches that donor dermal fibroblasts were isolated from an adult male guar. Enucleated bovine oocytes were obtained for nuclear transfer. Following NT, the fused complexes were then analyzed and the resulting blastocysts were transferred into recipient females. Three fetuses were analyzed for confirmation of genomic origin and fetal fibroblast cell lines were derived. These cells were cytogenetically analyzed and mitochondrial DNA and microsatelliteDNA was also analyzed. The specification teaches that cytogenetic analysis of the cloned cell strains revealed a normal karyotype with a chromosome number of 58, identical to the donor fibroblast (see p. 47, line 29). Microsatellite analysis showed that the cloned cell strains had *gaurus* nuclear background (see p. 48, lines 1-2). Analysis of the mitochondrial DNA (mtDNA) found that no *gaurus* mtDNA was present, and that the mtDNA was contributed to the bovine oocytes.

Applicants' arguments have been carefully considered, however, they are not found persuasive. Applicants state that Wolfe *et al.* disclose the generation of blastocysts from cross-species nuclear transfer units generated by transferring goat and bison cells into enucleated bovine oocytes. Applicants point out that Wolfe *et*

al. used embryonic goat and bison cells as donor cells and Applicants' invention is directed to differentiated donor cells which need to be reprogrammed by the oocyte cytoplasm to successfully direct embryogenesis [see p. 24-25 of Applicants' Response]. In response, it is noted that the Wolfe *et al.* reference was not provided under 112, 1st paragraph, but rather, under a 103 rejection. Applicants argue that because humans and bovines are so far removed from each other, one of skill in the art would reasonably regard the Applicants' demonstration that a blastocyst successfully generated from a nuclear unit produced by transferring a human differentiated cell into a bovine oocyte, and their successful isolation of a line of embryonic cells having the appearance of ES cells from such a blastocyst, would be strong evidence that other cross-species combinations using species that are more evolutionarily related would also yield similar results [see pp. 24-45 bridging paragraph of Applicants' Response]. Applicants point to various pieces of post-filing art to support this, in particular, Kitiyanant *et al.* describe the successful generation of blastocysts following transfer of nuclei of fetal buffalo fibroblasts into enucleated bovine oocytes, and Trivedi describes the generation of blastocysts of European mouflon [a species of sheep] into the enucleated oocytes of domestic sheep, Dayuan *et al.* teach the successful generation of blastocysts after nuclear transfer of somatic cell nucleic of the giant panda into enucleated rabbit oocytes and Dominko *et al.* teach the transfer of somatic, differentiated cell nuclei of sheep, pig and monkeys into bovine oocyte which led to a "blastocyst-like structure with distinct blastocyst morphology" [see p. 25, 2nd paragraph of Applicants' Response]. Applicants argue that as such, one of skill in the art would regard that the claimed invention is enabled as evidenced by Dominko *et al.* who state that embryonic cell lines grown from cross-species embryos, such as those of the present invention are

expected to be useful for evaluating, "long and short-term effects of mixing nuclear and cytoplasmic components of various species." [See pp. 25-26, bridging paragraph].

Applicants' arguments, as well as the cited post-filing art have been carefully considered, but they are not found to be persuasive. It is noted that post-filing art supports that nuclear transfer methodology may result in an embryo which contains both paternal and maternal mitochondrial DNA, however, heteroplasmy, as was seen with Dolly, was the result of same-species nuclear transfer. Heteroplasmy can occur between sub-species, as supported by Meirelles *et al.* [**Genetics**, 158:351-356, May 2001] and Shitara *et al.* [**Genetics**, 156:1277-1284, November 2000]. However, this phenomenon does not necessarily extend to every mammalian species, or to all cell types, which would be used for nuclear transfer [see Shitara *et al.*, *Discussion*, p. 1282]. Furthermore, the cited art of Meirelles *et al.* and Shitara *et al.*, clearly suggests that xenomitochondrial cybrids can be generated, however, due to incompatibilities and the inability of the cybrid to develop, the cross-species reconstituted embryos fail to develop [see Meirelles *et al.*, pp. 351-352, bridging paragraph]. Accordingly, in regard to xenomitochondrdial cybrids, as claimed by the present invention, the state of the art strongly suggests that even if the claimed invention resulted in an multicellular structure from which an embryonic cell could be isolated and cultured, the mitochondria present in the viable embryonic cells would be from the same species as the donor, *i.e.*, compatible.

Furthermore, it is reiterated that although the methods of the instant invention result in the production of 1 NT unit of which the specification reports propagates into what appears to be ES-like cell colonies (as determined by cell morphology) in Example 1, and the production of fetal mammals using interspecies

NT (Example 2), the specification fails to demonstrate that the ES-like cells function in Example 1 as true ES-cells in that they are in fact totipotent or that they function as stem cells in that they are capable of differentiation into other multilineage cell-types. As such, the specification fails to enable the production of embryonic or stem-like cells, which, in further dependent claims [see, for example, claim 75] would be further cultured to produce a cell line.

Applicants' arguments have failed to overcome the unpredictabilities found in the state of the art of the method of nuclear transfer, for reasons advanced on pages 6-7 of the prior Office action, mailed 1/30/02. In particular, the claimed invention is directed to "isolated embryonic cell(s)" which are produced by nuclear transfer methods. It is noted that embryonic cells encompass embryonic stem cells [both totipotent and pluripotent]. However, the specification does not provide teachings or guidance to demonstrate that the cells that are described by the specification as "ES-like" are true pluripotent cells (embryonic stem cells or embryonic or stem-like cells). Particularly, the specification fails to demonstrate whether the ES-like cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell types, or express exclusive ES cell markers. The specification only discloses several morphological characteristics (Example 1). Further, it is not predictable (without specific guidance) whether the described ES-like cells are even cells which are capable of differentiation upon induction to a particular cellular pathway, e.g., lineage or multilineage precursor. The specification teaches that the prior art is lacking in the production of inner cell mass cells from NT units useful to form ES cell-like colonies that could be propagated (page 6, lines 19-22). Thus, the skilled artisan would not have found guidance from the art on the methodology of nuclear transfer utilizing

differentiated adult human or mammalian cells or nuclei for insertion into bovine enucleated oocytes. For this, the artisan could **only** rely on the instant specification and in light of the very low frequency of NT units produced by the method, the lack of a showing demonstrating differentiation from the produced cells, and the lack of evidence demonstrating ES cell totipotency; the claimed invention is not enabled by the specification. Furthermore, as the claimed isolated embryonic cells(s) additionally encompass cells which are not totipotent or pluripotent, Applicants have not provided a use for such isolated embryonic cells. As such, it is unknown how the skilled artisan would be able "to use" the claimed isolated embryonic cells in a manner which is consistent with the specification without specific guidance.

Further, Applicants' arguments have not overcome the unpredictabilities in the art with regard to the species-specific differentiation of ES cells [see the prior Office action, pages 7-8]. As such, the specification fails to provide guidance and direction for critical parameters of the claimed invention with respect to obtaining true totipotent embryonic stem cells that give rise to germline tissue and the whole animal, or even embryonic cells which are merely capable of differentiation, for example.

It is reiterated that with regard to the structure and function of the cells produced by the NT methods of the invention, Dominko et al. (Biology of Reproduction, 1999 and cited by Applicant) support that cross-species NT cannot be judged as useful before nuclear reprogramming, somatic cell/recipient cytoplasm compatibilities are examined. See page 1501, last paragraph. With regard to examining nuclear reprogramming or dedifferentiation, Dominko et al. disclose that such can only be determined by demonstration of a pregnancy carried to term. As Dominko et al. only teach that bovine cytoplasm has the ability to support several

mitotic cell cycles directed by newly introduced nuclear DNA, importantly, they note that "[w]hether this introduced differentiated DNA is reprogrammed, is modified, or simply remains unchanged is currently under investigation." See page 1501, column 1, first paragraph. As such, in view of the supported undeveloped and unpredictable state of the art with respect to the characterization of cells produced by cross-species NT, Applicants' demonstration of the production of only one NT unit (Table 1) cannot be extrapolated to the production of embryonic stem cells as known in the art or as precursor cells as known in the art.

The courts have stated that:

A specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material or **of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.** Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to provide guidance to the skilled artisan on any parameters which would be necessary and critical for cross-species NT process from which embryonic cells [which include totipotent, pluripotent cells] can be isolated and cultured to produce cell lines.

Furthermore, the specification in particular, has not provided a use for isolated embryonic cells made by the method. Note that the term "embryonic cell"

encompasses embryonic stem [ES] cells and that true ES cells have the potential upon transfer to a host to develop into a human being. As certain of the product claims recite isolated embryonic cells which contain human genomic DNA, this argument is proper in that certain embodiments of the claimed invention encompass embryonic stem cells, which have a well-known potential in the art to give rise to the corresponding species of animal. It is acknowledged that the specification contemplates the production of human stem cell multilineage precursors, however, since the specification also discusses the ES cell potential for germ-line manipulation (pages 2-8) with respect to ES cells of non-human mammalian species, it is not clear how and under what circumstances, humans would be so made from the ES-like cells of the invention.

It is noted that it appears that the state of the art, as it specifically pertains to the instant application and claimed invention, is clearly lacking in supported evidence. In particular, Marshall (Nature, 1998) discloses that "Robl concedes that the experiment did not yield publishable data" (see col. 3, 1st full paragraph) and that [Robl] "classified the cells as human stem cells based on his experience of 'looking at hundreds and hundreds' of cell colonies." Marshall discloses, that at that time, none of the normal tests had been performed to demonstrate that these cells were human or that they were stem cells. Furthermore, Marshall reports that one skilled in the art, had stated that the cells in question had met none of the criteria for embryonic stem cells. As such, it would have required undue experimentation

for one skilled in the art to perform the claimed methods of NT transfer for production of cells which meet the criteria of a true embryonic stem cell, or rather a stem cell of sort, which upon differentiation, would provide cellular or gene therapy upon transplantation. A nexus must be provided between the production of their one NT unit and claims directed to "isolated embryonic cells".

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation for producing human or mammalian embryonic cells [encompassing embryonic stem cells] which are capable of mere differentiation, for example, the unpredictable and undeveloped state of the art with respect to cross-species nuclear transfer (using adult differentiated nuclei) for production of isolated embryonic cells [of which, embryonic stem cells are encompassed] which give rise to germline tissue and the whole animal or which may be induced to differentiate, in particular with respect to carrying out a process involving insertion of differentiated, adult human cell nuclei into bovine oocytes, the unpredictable state of the art with respect to extrapolating results obtained from ES cells of different species of animals to results obtained from chimeric bovine/human embryonic or stem-like cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-82, 86-116 and 125-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51, as written, is unclear. The claim recites "removing the genomic DNA from a mammalian oocyte" in part (i) of the claim. It is unclear what this step encompasses, and further, it is noted that in the nuclear transfer art, only *enucleation* of the mammalian oocyte would result in a successful nuclear transfer unit. Claims 52-82 and 125-132 depend from claim 51.

Claim 86, as written is unclear. The claim recites "removing the genomic DNA from a mammalian oocyte" in part (i) of the claim. It is unclear what this step encompasses, and further, it is noted that in the nuclear transfer art, only *enucleation* of the mammalian oocyte would result in a successful nuclear transfer unit. Claims 87-116 depend from claim 86.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 79-85, 112-124, 128-132 are rejected under 35 U.S.C. 102(b) as being anticipated by Heyneker *et al.* [WO 91/08216, published 13 June 1991].

The claims are directed to an isolated embryonic cell wherein the cell is not itself an embryo, and isolated cells. In further embodiments, the isolated embryonic cell or isolated cell can have the following combinations: non-bovine genomic DNA and bovine mitochondria, human genomic DAN and mitochondria of a non-human mammal, human genomic DNA and bovine mitochondria, genomic DNA of one species of mammal and mitochondria of a different species of mammal, human genomic DNA and non-human mitochondria, and human genomic DNA and bovine mitochondria. In further embodiments, the genomic DNA of the isolated embryonic cell is genetically altered by the addition, modification, substitution, or deletion of one or more genes that encode an enzyme, growth factor or a cytokine.

Note that claims 79-85, 112-126 and 128-132 are product by process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or

inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Heyneker *et al.* teach the generation of transgenic bovine species comprising a transgene encoding a recombinant DNA sequence, wherein the recombinant DNA sequence can encode human polypeptides such as industrial enzymes such as proteases, lipases, chitnases, etc. [see p. 12, 1st paragraph]. Heyneker *et al.* teach methods of generating the transgenic bovine species [see p. 28-29] and teach that before the transgenic embryos are implanted into recipient females, one cell is removed from each of the embryos and treated to release the DNA contained therein. Each of these released DNAs are then digested to verify the presence of the transgene [see p. 8, lines 11-24]. As such, Heyneker *et al.* teach the limitations of

the claims, because a transgenic cell that is isolated from an embryo would have genomic DNA which would include the human transgene, and mitochondria bovine DNA. As such, Heyneker *et al.* teach cells which are genetically altered with genomic DNA from a different species [human] than the mitochondrial DNA [bovine].

As such, Heyneker *et al.* anticipate the claimed invention.

Claims 79, 81, 83, 84, 112, 114, 117, 118, 121, 123, 128, 130 are rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi [**Scientific American**, March 1994, 270:34-41].

Capecchi teaches knockout technology applied to mice, specifically with respect to the disruption of the *Hox*A-3 gene utilizing homologous recombination and as a method of producing the same, applies to determining the *in vivo* biological function of any known gene of interest. Capecchi further discloses the essential components of a targeting vector [p. 38, col. 3, and p. 39, col. 1-2], and the steps involved for targeted gene replacement in ES cells as well as in mice [see p. 36-39 and diagrams]. Capecchi teaches the limitation of the claimed invention, as the transgenic ES cells would have genomic DNA from both mouse and the human [due to the human transgene] and mitochondrial DNA from the mouse. As such, the genomic and mitochondrial DNA in the transgenic ES cells would be of different species.

Accordingly, Capecchi anticipates the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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